Remarks

By the present amendment, claims 4, 9-10, and 15-16 are revised to address issues raised in the Final Office Action. No new matter is entered by these amendments. The amendment also cancels claims 48-49 without prejudice or disclaimer. Applicant reserves the right to pursue the canceled subject matter in one or more applications with the same rights of priority as the instant application.

Applicant respectfully urges entry of these amendments after final because the revisions do not necessitate a further search, and they place the claims in condition for allowance or, at least, in better condition for appeal.

The Final Office Action dated July 12, 2006, has been carefully considered. The amended claims and the following comments are believed to represent a complete response and to place the application in condition for allowance. Reconsideration is respectfully requested, therefore.

§112, Second Paragraph, Rejections

Claim 4 was rejected for a clerical error in referencing step "c" instead of step "d". Applicant has amended claim 4 to reference step "d" as suggested in the Action. Entry of this amendment and withdrawal of this rejection therefore is respectfully requested.

Claims 48 and 49 were rejected for allegedly being confusing, in view of the previous amendments to claim 1, from which they depend. The cancellation of these claims obviates this rejection.

35 USC §112, First Paragraph – Written Description

Claims 1, 4-10, 12-16, 18-19 and 48-50 stand rejected for alleged lack of written description with respect to the term "non-human host cell." Applicant respectfully traverses this rejection.

Page 4 of the Action acknowledges that the specification teaches the use of non-human host cells, such as bacterial cells, insect cells, yeast cells, and plant cells, as host cells. Nevertheless, the Action cites MPEP § 2173.05(i) for the proposition that "[a]ny negative limitation . . . must have basis in the original disclosure," apparently reading this provision as imposing a requirement for support in haec verba for a negative proviso. Yet the MPEP imposes no such requirement, which would contravene settled law on the written description requirement.

As noted in MPEP § 2173.05(i), "there is nothing inherently ambiguous or uncertain about a negative limitation." The MPEP does state that "[a]ny negative limitation . . . must have **basis** in the original disclosure," but this does not require support in haec verba. To the contrary, the MPEP explains that "a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a prima facie case for lack of descriptive support," and cites MPEP § 2163 for further information. The latter provisions plainly state that "the subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement." Instead, it explains, the "fundamental factual inquiry" for written description "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed."

MPEP § 2163.04 sheds further light on this issue, requiring that a rejection for lack of written description include "reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of

the invention as claimed in view of the disclosure of the application as filed." The rejection here fails to include such reasoning.

The specification provides ample support for the recitation of a "non-human host cell," and clearly conveys to the skilled artisan that Applicant had possession of the claimed invention at the time of filing. At noted at page 4 of the Action, the specification (page 7, lines 3-4) teaches that bacterial cells, insect cells, yeast cells, plant cells and mammalian cells are suitable as host cells. The specification additionally teaches that the protein "may also be produced in an edible food source, such as animal milk, or in an edible crop." Specification, page 13, lines 27-29. Applicant respectfully submits that these teachings, particularly when read in view of the disclosure as a whole, plainly convey to the skilled artisan Applicant's possession of the invention with regard to non-human host cells. Indeed, because aspects of the invention relate to "methods for recovering recombinantly produced polypeptides," (see, e.g., Specification, pg. 1, lines 3-4, & Abstract), those skilled in the art surely would understand that references to "mammalian" host cells includes "non-human" host cells, particularly in view of the reference to production in "animal milk."

Only an imposition of an in haec verba requirement, in contravention of the PTO's own rules, could substantiate a written description rejection keyed to the present recitation of "non-human" host cells. Precisely because such a requirement is contrary to law, the present rejection of claims 1, 4-10, 12-16, 18-19 and 48-50 is improper and should be withdrawn.

35 USC §112, First Paragraph – Enablement

Claims 1, 4-10, 12-16, 18-19 and 48-51 were rejected for alleged lack of enablement. Applicant respectfully traverses this rejection.

While acknowledging that the claimed invention is enabled with respect to recombinant production in an isolated host cell or in a bacteria, yeast or insect cell, the Action continues to question enablement with respect to recombinant production in "any non-human host," or in "any plant." Applicant respectfully maintains its position that the full scope of the pending claims is enabled.

The Action continues to focus improperly on the enablement of "gene transfer." The present invention relates to the discovery that a recombinant polypeptide of interest can be obtained by methods comprising recombinantly producing a fusion protein comprising a full-length chymosin pro-peptide and the polypeptide of interest, and contacting the fusion protein with a mature form of an autocatalytically maturing aspartic protease that is capable of cleaving the chymosin pro-peptide from the fusion protein to release the recombinant polypeptide. While the claimed methodology involves the recombinant production of proteins in a host cell, recombinant protein production per se is not the focus of the invention. Indeed, the evidence of record demonstrates that the state of the recombinant protein production art was advanced at the time the application was filed.

As set forth in MPEP § 2164.03, the "more that is known in the prior art about the nature of the invention . . . the less information needs to be explicitly stated in the specification." Indeed, MPEP § 2164.05(b) provides that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." In keeping with these guidelines, the instant specification was not required to provide detailed teachings and examples of recombinant protein production in various host cells, because that information was known in the art and readily available to the skilled artisan at the time of filing, as demonstrated by the numerous representative references submitted with Applicant's previous response.

That the Examiner was able to uncover three articles that discuss ongoing issues in the field of recombinant protein production does not show that it would have required an undue amount of experimentation for someone skilled in the art to practice the invention. Instead, these articles support Applicant's position as to the advanced state of the art, because they address issues that have arisen as recombinant protein production has moved out of the research laboratory into the commercial world.

The Action cites Dyck for stating that "the generation of transgenic domestic animals is difficult . . ." and that "current methods . . . are relatively inefficient and time-consuming" (emphasis added). These alleged problems are purely commercial considerations that have no bearing on the enablement of the claimed methods. Indeed, the entire focus of Dyck is the evaluation of various transgenic systems as "bioreactors" for large-scale production of proteins, and Dyck starts with the premise that "[t]he ability of transgenic animals to produce complex, biologically active recombinant proteins . . . has stimulated a great deal of interest in this area."

Dyck itself cites numerous categories of successful transgenic protein production, including transgenic milk ("Foreign proteins are commonly reported to be expressed in transgenic milk at rates of several grams per litre," pg. 395); the blood of transgenic pigs ("[P]igs producing human haemoglobin in their own circulatory system have been produced," pg. 395); methods using retroviruses ("[R]etroviruses have been used to successfully produce transgenic mice and viral integration of recombinant sequences into bovine embryos to produce transgenic calves have been reported," pg. 396); methods using embryonic stem (ES) cells or primordial germ (PG) cells ("Reviews of the literature indicate that the production of chimeric animals with ES or PG cell technology has been applied successfully in mice, rabbits, pigs, cattle and poultry," pg. 397), and methods using pronuclear microinjection, which Dyck characterizes as being "the most straightforward and consistently successful means of gene transfer for most species" (pg. 397). This is hardly evidence of non-enablement.

The Action cites Vain for stating that "transgene expression in plants remains largely unpredictable," but that statement is taken out of context. Reading the complete sentence (at pg. 878, col. 2) reveals that the "unpredictable" factors being noted are "variation in expression levels and stability between independently transformed plants," not the ability to achieve transgenic expression per se. In Vain's own experiments, 100% of 95 independently transformed rice plants successfully expressed one of two transgenes, and 87% expressed both transgenes. Thus, Vain does not support an assertion that undue experimentation is required to produce transgenic proteins in plants. Instead, Vain's focus is on transgene behavior in the progeny of transformed plants, an issue that is wholly irrelevant to the enablement of the instant claims.

The Action cites Potrykus for the premise that gene transfer in cereals is largely unsuccessful, but the Action's reliance on this article to support an enablement rejections is misplaced. Potrykus presents an admittedly "subjective" review of different methods that have been used to effect gene transfer in cereal crops "and their potential agronomic utility" (emphasis added). Thus, this article, like those discussed above, relates to issues encountered on the road to commercialization. While Potrykus criticizes a number of different transgenic methods, it also acknowledges methods that have proven successful, including methods using agrobacterium or agroinfection to transform dicots and methods using protoplasts for direct gene transfer of cereals. In fact, the "Note added in proof" at page 542 reports Potrykus' own work to establish "what we believe is proof of the recovery of transgenic offspring of Indica-type rice." That work, reported in Datta et al., Bio/Technology (1990) 736-40 (copy attached), is said to result in "a simple and reproducible method of transformation of an important food crop." Thus, Potrykus does not undermine the enablement of the present invention with respect to recombinant protein production in plants.

Applicant also questions the validity of Potrykus as an accurate reflection of the state of the art. As noted above, Potrykus itself states that it presents a "subjective" discussion. Moreover, Potrykus admits that it includes "several statements. . . for which no solid

experimental data are available." The evidentiary value of Potrykus' critiques therefore pales in view of the numerous references of record that present scientific data demonstrating the successful production of transgenic proteins in plants, including Potrykus' own work.

In citing Dyck, Vain and Potrykus against Applicant, the Action loses sight of the fact that § 112 does not require an applicant "to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment." MPEP 2164. All that § 112 requires is that the specification enable those skilled in the art to practice the claimed invention without an undue amount of experimentation. Because Applicant has demonstrated that recombinant protein production in a wide variety of hosts (including animals, bacteria, insects and plants) was well-developed at the time the present application was filed, the instant enablement rejection is improper, and should be withdrawn.

35 USC §103

The Action maintains the following obviousness rejections:

the rejection of claims 1, 4, 6-9, 13, 15, 19 and 51 over Ward in view of Walsh and Yonezawa;

the rejection of claim 5 over Ward, Walsh and Yonezawa, and further in view of Fine, as set forth in the previous Action; and

the rejection of claims 14 and 50 over Ward, Walsh, and Yonezawa, and further in view of Dunn.

Applicant respectfully traverses these rejections for the reasons set forth in Applicant's previous responses, as supported by the Declaration of Dr. Moloney. As stated previously, there is simply no teaching or motivation in the prior art of preparing a recombinant polypeptide of interest by producing a fusion protein comprising a chymosin pro-peptide and the polypeptide of interest, and using a mature aspartic

protease to cleave the chymosin pro-peptide sequence from the fusion protein to release the recombinant polypeptide of interest, as claimed. As demonstrated previously, those skilled in the art had no reasonable basis for expecting that an aspartic protease would be capable of cleaving a chymosin pro-peptide from a fusion protein to release the recombinant polypeptide, and did not know, for example, whether the aspartic protease would cleave the recombinant polypeptide at undesired sites and/or would cleave off too many or too few amino acid residues around the junction between the pro-peptide and the recombinant polypeptide. Without an assurance of accurate cleavage, there was no motivation to have employed an aspartic protease as presently claimed.

Because it is only the instant specification that recognizes and teaches that aspartic proteases are capable of cleaving a chymosin pro-peptide from a fusion protein to release a recombinant polypeptide of interest, these obviousness rejections are improperly founded on hindsight, and should be withdrawn.

The Action newly rejects claims 10 and 16 as obvious in view of Ward, Walsh and Yonezawa, and further in view of Huber (U.S. Patent No. 4,180,559) and Fan (U.S. Patent No. 4,774,183). The Action explains that this rejection is based on an interpretation of claims 10 and 16 that does not require step d) of the recited method to be effected in vivo, but that reads those claims as encompassing methods effected in vitro, but under "in vivo conditions." Applicant believes that the foregoing amendments to claims 10 and 16 obviate this rejection. As amended, claims 10 and 16 recite that "step d) is effected in vivo." Because the cited references do not teach or suggest such a method, the obviousness rejection should be withdrawn.

CONCLUSION

In view of the foregoing, we submit that the application is in order for allowance and an early indication to that effect would be greatly appreciated. Should the Examiner like to

discuss the matter, he is kindly requested to contact Micheline Gravelle at 416-957-1682, or Courtenay Brinckerhoff at 202-295-4094, at his convenience.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to our Deposit Account No. 02-2095.

Respectfully submitted,

By Courtenay C Brinckerhoff
Micheline Gravelle Reg No 37,288
Reg. No. 40,261

Bereskin & Parr
Box 401, 40 King Street West
Toronto, Ontario
Canada M5H 3Y2
Tel: 416-957-1682
Fax: 416-361-1398